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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/523,809	03/13/2000	Michael P. Murphy	686.03.498CON	6553

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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1636	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/523,809	Applicant(s) MURPHY ET AL.	
	Examiner S. Kaushal	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

The request filed on 04/03/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/523,809 is acceptable and a CPA has been established. An action on the CPA follows.

Claims 1-30 were pending and were examined in this office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

► *If the claims are amended, added and/or canceled in response to this office action the applicants are required to follow Amendment Practice under 37 CFR § 1.121 (http://www.uspto.gov) and A CLEAN COPY OF **ALL** PENDING CLAIMS IS REQUESTED.*

Claim Rejections - 35 USC § 112

Claims 1-30 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the same reasons of record as set forth in the official action mailed on 07/03/01.

Claims 1, 8, 9, 16, 19, 24, 27 and 29 recite limitation "exogenous matrix components" and "synthetic members". The metes and bounds of "exogenous matrix components" and "synthetic members are not clear. It is unclear what is the nature (chemical or biological structure) of "exogenous matrix components". Similarly, it is unclear what is encompassed by

"synthetic members". The broadest reasonable interpretation of a synthetic member encompass any non-naturally occurring polymer and any and all types of tissue supports.

Claims 7 and 21 are indefinite because it is unclear what are the metes and bounds of a culture medium containing "no non-human components". It is unclear whether this includes any chemical or protein, to include essential and non-essential amino acids, which are not produced in the human body or required for its proper functioning?

Claims 19-23 and 24-26 are indefinite because it is unclear what are the steps involved in "stimulating the fibroblast cells to synthesize, secrete, and organize extracellular matrix components". The invention as claimed fails to recite the required step. It is unclear what is the stimulation that causes the fibroblasts to secrete and organize extracellular matrix components in this context.

Claims 1-18, 28 and 30 are unclear as to the metes and bounds of cultured "under conditions to produce a layer of extracellular matrix". It is unclear what are the conditions that lead to production of extracellular matrix in this context.

Claim Rejections - 35 USC § 103

Claims 1-3, 6-12, and 19-27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bell, E. (US Patent 4,485,096), in view of Parenteau et al (US Patent 5,712,163), Sand, BJ (US Patent 5,618,284), Holbrook et al (1993) and Biegel et al (1994) for the same reasons of record as set forth in the official action mailed on 07/03/01.

Bell, E teaches the use *in vitro* of human foreskin and dermal fibroblasts cultured in Falcon bacteriological dishes comprising McCoy's 5a medium, Fetal Calf Serum, NaOH, and a collagen solution to form a contractable, transplant tissue and wherein a layer of keratinocytes may be added *in vitro* (claims 15 & 16; and Example 1, col 8, lines 39-55, col 3, lines 28-30). Bell also teaches the method of tissue transplantation in guinea pigs and rats (e.g. Examples 10 and 11). Bell et al does not teach the use of chemically defined media, the molecular

composition of the differentiated tissue, e.g. collagen, decorin, and GAG, or the use of said procedure in the absense of exogenous matrix components (e.g. collagen).

Parenteau et al teach the use of a chemically defined cell culture medium (see col. 10-16) which by definition are absent of undefined proteins from protein supplements such as serum, and wherein the cell culture systems comprise said cell culture medium and a substrate for the cells, such as glass or plastic, and in the absence of exogenous matrix components or synthetic membranes which resulted in the prolonged growth and differentiation of cells, such as keratinocytes (e.g. col. 1, lines 35-55, claims 20 and 24). Parenteau clearly teaches the culturing of human karatinocytes on plates NOT coated with collagen (col.24, example-5). Parenteau et al also teach the method of producing skin equivalents grafts in vitro utilizing keratinocytes and dermal (fibroblast) equivalents (example 6, col 25, line 61-col 26, line 14), and the use of a sequential two culture medium process in the absence of a substrate which showed only a slight decrease in plating efficiency in comparison to those that were grown on a collagen substrate (e.g. Table 5, col 5).

In addition, Sand, BJ teaches that human type-1 collagen molecule consists of chains of 300 nm triple helixes joined by 67nm uncoiled bonds (col 10, lines 32-33). Holbrook et al teach that the dermal matrix of connective tissue is comprised of collagen, of which 80-90% is type I and 8-12% is type III, glycosaminoglycan, fibronectin, and tenascin (pg 117, col 1, para 3 & pg 119, col 1, para 1 and 3). Biegel et al teach the use of the Transwell filters coated with hydrated collagen gels for the use in growing endothelial cells in vitro which resulted in monolayers growing until confluency and exhibiting biochemical, morphological, and electrophysiological properties reflective of cells in vivo (abstract).

In light of Bell, Parenteau, Sand, Holbrook and Biegel et al it would have been obvious to one of ordinary skill in the art to make a cultured tissue construct comprising fibroblast cells, such as neonate male foreskin or dermal, grown under a sequential cell culture conditions on a Transwell plate coated with collagen to produce a layer of extracellular matrix comprising type I and III fibrillar collagen, glycosaminoglycan, decorin, fibronectin, and tenascin and wherein said cells are cultured in the absence of exogenous matrix components in a chemically defined media containing no non-human components and comprising a second layer of epithelial cells, such as keratinocytes; and utilizing said construct for transplanting in an animal model. Furthermore,

Parenteau teaches that cells can be cultured on glass or plastic, and in the absence of exogenous matrix components like collagen. Parenteau et al also teach the culturing of human karatinocytes on plates NOT coated with collagen (col.24, example-5). Furthermore the percentage of cell confluence, the thickness of the resulting matrix, and the density of the seeded cells are rate effective variables which one of ordinary skill in the art could readily ascertain through routine experimentation.

One would have been motivated to utilize a tissue construct in the absence of exogenous matrix components to provide an efficacious method of dermal regeneration which did not require the construction of a biodegradable matrix, and to utilize a chemical defined medium to optimize tissue differentiation and growth (Parenteau et al, col 1, lines 35-55). One would also have been motivated to use a porous membrane, such as Transwell plates, because the layer of collagen (or polycarbonate membrane) on the plates would allow for the efficacious adhesion and differentiation of fibroblast cells, especially in light of the absence of an exogenous extracellular matrix scaffold. There would be a reasonable expectation of success because Bell demonstrated that tissue constructs could be generated utilizing a base layer of fibroblasts with a top layer of keratinocytes to generate full thickness skin grafts and done in the absence of three dimensional matrices (e.g. Bell, claim 16) and because Parenteau et al had demonstrated the successful use of tissue constructs comprising keratinocytes using said defined culture medium and in a sequential two step culture system and without any collagen coating and because Biegel et al had demonstrated the sucessful use of the Transwell system for in vitro growth and differentiation of endothelial cells into tissue (e.g. Parenteau et al, Example 5, col 24, lines 35-40, & Biegel et al, abstract).

Claims 1, 4, 5, 9, 13, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jahoda et al (1993) in view of Parenteau et al (US Patent 5,712,163) for the same reasons of record as set forth in the official action mailed on 10/12/00.

Jahoda et al teach that the transplantation of dermal papilla cells in rat ear wounds resulted in the production of hair growth in comparison to a control of transplanted skin fibroblasts, which resulted in no new hair growth (abstract and pg 585, col 1, para 1-3 and Table

1). Although, Jahoda et al does not teach the use of a cultured tissue construct system grown in-vitro to produce extracellular matrix components, Parenteau cured this deficiency.

Parenteau et al teach the use of a chemically defined cell culture medium, which by definition are absent of undefined proteins from protein supplements such as serum, and wherein the cell culture systems comprise said cell culture medium and a substrate for the cells, such as glass or plastic, and in the absence of exogenous matrix components or synthetic membranes which resulted in the prolonged growth and differentiation of cells, such as keratinocytes,(e.g. col 1, lines 35-55, claims 20 and 24). Parenteau et al also teach the method of producing skin equivalent grafts in vitro utilizing keratinocytes and dermal (fibroblast) equivalents (example 6, col 25, line 61-col 26, line 14), and the use of a sequential two culture medium process in the absence of a substrate which showed only a slight decrease in plating efficiency in comparison to those that were grown on a with or without collagen substrate (e.g. Table 5, col 5).

Thus in light of Jahoda and Parenteau et al, it would have been obvious to one of ordinary skill in the art at the time of the invention to create a cultured tissue construct comprising dermal papilla cells with fibroblast cells and with or without a top layer of epithelial cells, such as keratinocytes. One would have been motivated to do this to provide a method of producing a tissue construct that could be used to generate new hair growth (Jahoda et al, Table 1). There would be a reasonable expectation of success because Jahoda et al demonstrated the ability to culture dermal papilla cells in MEM containing fetal bovine serum and L-glutamine and then transplant them into rats for successful production of hair and the culturing and implantation of fibroblasts for successful production of dermal skin, while Parenteau et al had demonstrated the ability to culture keratinocytes in the absence of exogenous matrix components and synthetic membranes to produce differentiated, stratified tissue (Parenteau et al, abstract). Thus the invention as claimed is *prima facie* obvious in view of prior art of record.

Conclusion

No claims are allowed.

This is a CPA of applicant's earlier Application No. 09/523,809. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Irem Yucel Ph.D. can be reached on (703) 305-1998. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Zeta Adams, whose telephone number is (703) 305-3291.

S. Kaushal
Patent examiner

Scott D. Priebe
SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER